Summary

Oncogenes, tumor suppressor genes, and apoptosis-inducing genes play critical roles in cell proliferation, differentiation, and death. Their expressions are frequently altered in cancer cells by gene mutation, deletion, rearrangement, inactivation, or overexpression. Some of these alterations are directly related to the development and maintenance of malignant phenotypes; others relate to the response of cancer cells to various anticancer therapies. Both preclinical and clinical studies have indicated that restoring the normal function of these genes may be an effective means of cancer therapy although full realization of any anticancer benefit will depend on effective delivery of these genes to cancer cells.

Key Words: Gene therapy; neoplasia; apoptosis; oncogene; tumor suppressor gene; adenovirus.

1. INTRODUCTION

A fundamental feature of cancer is the loss of normal cell behavior (i.e., cell proliferation, differentiation, and death), resulting in the unlimited and continuous growth of cancer cells. Because this malignant phenotype can be inherited by the offspring of cancer cells, it is widely considered that cancer is a genetic disease of somatic cells and that genes which regulate cell growth, cycling, differentiation, and death are frequently altered or mutated (1,2).

Stepwise development of malignant phenotype is another well-recognized feature of cancer (2). Premalignant lesions have been observed for several types of cancer. For example, in the familial adenomatous polyposis (FAP) syndrome, a large number of precancerous colonic polyps may develop in affected individuals between 7 and 36 yr of age,
and without colectomy, will inevitably lead to colon cancer (3). Another example is myelodysplasia syndromes (MDS), which are clonal stem cell disorders characterized by progressive cytopenia and the presence of multilineage dysplasia in bone marrow. It is estimated that between 20 and 40% of adults with MDS will develop acute leukemia (4).

Because cancer is considered a genetic disease, its stepwise development must involve distinct gene alterations in at each step of cancer development (1,2). Moreover, it has long been realized that in normal situation, cell growth is under control of two distinct groups of signals. Oncogenes normally encode positive signals that promote cell growth and division. Tumor suppressor genes normally encode negative signals that inhibit cell growth and division and induce cell-cycle arrest or initiate apoptotic programs. Apoptosis-related genes encode a variety of gene products that promote either cell survival (antiapoptotic) or cell death (proapoptotic). The resulting progrowth and antigrowth and proapoptotic and antiapoptotic functions collectively determine the cell’s fate to grow or not to grow, to die or not to die. Any dysfunction or imbalance of these signals may lead to abnormal cell behavior and malignant transformation (7,8).

2. ONCOGENES

2.1. Viral Oncogenes

The concept of oncogenes initially came from studies of neoplastic transformation by tumor-producing viruses. As early as the 1960s, it was noticed that some DNA or RNA viruses could induce tumor formation either in their natural hosts or in heterologous species (9,10). Among the RNA viruses, only retroviruses can induce neoplastic transformation. Some retroviruses, such as the avian leucosis virus (ALV), can induce tumor formation only after long incubation periods, usually lasting more than several months. Other retroviruses, such as the Rous sarcoma virus (RSV), can induce tumor formation very rapidly in infected chickens, usually within 1 to 2 wk, and are thus named acute transforming viruses. Comparison of the genome of acute transforming virus RSV with that of nonacute transforming virus ALV resulted in the discovery of the first viral oncogene (src), consisting of an extra gene sequence on the 3'-end between the env gene and 3'-long terminal repeats (LTRs) (11). Gene transfer experiments demonstrated that this additional gene could induce neoplastic transformation in chickens. Since then, more than 20 viral oncogenes have been identified and isolated from acute transforming retroviruses (12).

2.2. Proto-Oncogenes and Cellular Oncogenes

Although viral oncogenes can induce neoplastic transformation in animals, their mechanisms for doing so do not involve viral replication. This suggests that viral oncogenes are not necessary for viral life cycles and that they derive from other species. In fact, some early researchers observed that animals occasionally developed tumors very rapidly when they were infected with nonacute transforming retroviruses such as ALV. These nonacute transforming retroviruses were then isolated from the tumor sites and were subsequently shown not to be novel retroviruses but rather contained additional gene sequences in the genome. This finding strongly indicated that viral oncogenes derived from hosts that the viruses had infected. Direct evidence in support of this hypothesis came from DNA hybridization experiments. Isotope-labeled viral oncogenes, such as src, hybridized to DNA samples from a broad range of species including chicken, dog, and human.